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10/584,781	05/09/2007	Sungho Jin	15977-34	7355

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EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,781	JIN ET AL.	
	Examiner	Art Unit	
	PETER J. REDDIG	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *12,18-20,23 and 26-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-17,21,22,24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/7/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Election filed 05/03/04 in response to the Office Action of April 3, 2009 is acknowledged and has been entered. Applicant's election without traverse of Group I, claims 1-25 and the Species A2 - directed to nanoparticles with medication and a heat sensitive reservoir of medication, wherein the medication is released by heat; Species B1 - directed to targeting molecule(s) comprising an antibody; and Species C1 - directed to diseased cells relating to cancer is acknowledged.

2. Claims 1-28 are pending.

3. Claims 12, 18-20, 23 and 26-28 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-11, 13-17, 21, 22, 24, and 25 are currently under consideration.

Oath/Declaration

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Claim Objections

6. Claim 14 is objected to because of the following informalities: there are two periods at the end of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-11, 13-17, 21, 22, 24, and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating diseased cancer cells in a human or other animal body comprising the steps of: providing particles comprising nanoparticles of magnetic material, wherein the particles comprise medication introducing the particles into the body; directing the particles into or adjacent the diseased ceils; and applying a magnetic field to the magnetic nanoparticles to treat the diseased cells by magnetically induced release of the medication *does not* reasonably provide enablement for a method of treating diseased cancer cells in a human or other animal body comprising the steps of: providing particles comprising one or more nanoparticles of magnetic material, wherein the particles comprise medication introducing the particles into the body; directing the particles into or adjacent the diseased ceils; and applying a magnetic field to the magnetic nanoparticles to treat the diseased cells by magnetically induced motion of the nanoparticles, wherein the magnetic field rotates or laterally oscillates the nanoparticles to mechanically damage disease cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations."

(Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method of treating diseased cells (cancer) in a human or other animal body comprising the steps of: providing particles comprising one or more nanoparticles of magnetic material, wherein the particles comprise medication introducing the particles into the body; directing the particles into or adjacent the diseased ceils; and applying a magnetic field to the magnetic nanoparticles to treat the diseased cells by magnetically induced motion of the nanoparticles or by magnetically induced release of the medication.

The specification teaches that this invention provides two approaches to diseased cell destruction, (1) magneto-mechanical disturbance of cell structure (e.g. cancer cells) for cell lysis and (2) magnetically activated drug release at local regions (e.g. tumors) from a magnetic particle-containing drug reservoir, see p. 3-lines 10-15. The specification teaches that nanoscale magnetic particles can be targeted to diseased cells by tagging with biomolecules, guided with external magnetic fields, transfer magnetic energy for hyperthermia, and be detected by MRI, see p. 5 and 6. The specification teaches that magnetic particles move in a magnetic field and thus can be made to rotate or oscillate laterally back and forth, see p. 8-lines 9-12. The specification presents a hypothetical model of using elongated magnetic nanoparticles to mechanically induced damage to diseased cells, see p. 12 and 13 and Fig. 4.

One of skill in the art cannot predictably extrapolate the teachings of the specification to the enablement of the scope of the claims because the specification has not provided sufficient guidance or exemplification to use magnetic nanoparticles to mechanically damage diseased cells because it is well known the art that development of novel cancer therapeutics is unpredictable.

In particular, it is well known that the art of anti-cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models that only 29 have actually been shown to be useful for chemotherapy (p. 1041, see 1st and 2nd para.). Furthermore, Kaiser (Science, 2006, 313: 1370) teaches that 90% of tumor drugs fail in patients, see 3rd col., 2nd to last para. Because of the known unpredictability of the art, in the absence of experimental evidence in an appropriate animal model, with data commensurate in scope with the invention claimed, no one skilled in the art would accept the assertion that the claimed magnetically induced rotation or oscillation of the magnetic nanoparticles would predictably treat diseased cancer cells or the diseased cells of any other disease. Furthermore, the specification teaches that cells are a few to a hundreds of microns in size, see p. 5-lines 10-14, which is substantially larger than the nanometer scale particles claimed and thus it is not predictably clear that the oscillation or rotation of the nanoparticles would have sufficient mechanical force to damage the much larger cells. Although, magnetic particles have been used for drug delivery and the induction of hyperthermia (see the teachings of below Alexiou et al. (Cancer Research Dec. 2000, 60: 6641-

6648), Jordan et al. (J. Magnetism and Magnetic Materials, 2001 225:118-126, IDS), and Shinkai et al. (Jpn. J. Cancer Res. 92:1138-1146)), neither the specification nor the prior art has established a nexus between the motion of the magnetic particles and mechanically induced damage to cells. Furthermore, the specification has not taught what magnetic field would be sufficient to induce a rotation of the particles that would damage diseased cells *in vivo*. Although Babincová et al. (Med. Hypotheses 2000 55: 459-460) teach that the ideal frequency range for alternating magnetic field to induce hyperthermia with magnetic nanoparticles in 100-1000 kHz (see p. 460-2nd col.) the claims encompass any magnetic field frequency and specifically claim magnetic field frequencies as low as 1 Hz. Thus one of skill in the art cannot predictably use the broadly claimed method because no guidance has been provided as to what magnetic fields will be sufficient to rotate the magnetic nanoparticles and induce mechanical damage to diseased cells. Furthermore, the claims encompass using one or more nanoparticles of magnetic material and it would not predictably be expected that a single or few magnetic particles would be sufficient to treat cancers as cancers contain easily contain several orders of magnitude more cells. Additionally, one of skill in the art would not predictably expect to treat diseases that are not characterized by malignant cells, such as heart disease, diabetes, or neurological disorders by damaging or destroying cells as the cells do not necessarily need to be damaged or destroyed to treat the disease. Thus, for the reasons set forth above, undue experimentation would be required to make and use the method as broadly claimed for the treatment of cancer or any other disease.

Additionally, the claims encompass particles with targeting molecules attached. Although targeting molecules are known in the art, (see Shinkai et al. (Jpn. J. Cancer Res. 92:1138-1146), Alexiou et al. (Cancer Research Dec. 2000, 60: 6641-6648, see p. 6648), and Åkerman et al.

(Proc. Natl. Acad. Sci. USA, October 1, 2002 99:12,617-12,621, see Abstract and Fig. 1)) it would not predictably be expected that targeting molecules, such as antibodies, directed to targets other than molecules on the surface of cancer cells or other diseased cells would predictably be effective for targeting the nanoparticles to the diseased cancer cells or other diseased cells. In particular, White et al. (2001, Ann. Rev. Med., 2001, 52:125-145), teach that, for a successful targeting and immunotherapy, besides specificity of the antibody for the antigen, other prosperities of the antigen should be considered including the following: (1) the antigen should be present on all or near all of the malignant cells to allow effective targeting and to prevent a subpopulation of antigen-negative cells from proliferating; and (2) whether antigens are shed, modulated, or internalized influences the effectiveness of the administered immunotherapy (i.e. the antibody) (p.126, 2nd para.). Thus, for the targeting molecules/antibodies to predictably be effective without undue experimentation, the targeting molecules/antibodies should be directed to targets present on the surface of the majority of the diseased cancer cells.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and

the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as broadly claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-7, 10 and 11 are rejected under 35 U.S.C. 102(a) as being anticipated by Alexiou et al. (J. Drug Targeting, April 2003, 11: 139-149).

The claims are drawn to a method of treating diseased cells in a human or other animal body comprising the steps of: providing particles comprising one or more nanoparticles of magnetic material, wherein the particles comprise medication introducing the particles into the body; directing the particles into or adjacent the diseased cells; and applying a magnetic field to

the magnetic nanoparticles to treat the diseased cells by magnetically induced motion of the nanoparticles or by magnetically induced release of the medication.

It is noted that given that claims encompass effecting the delivery of the medication to the disease cells by application of the magnetic field and directing the particles into or adjacent the diseased cells by magnetic navigation, thus the treatment of the diseased cells by magnetically induced motion of the nanoparticles encompasses effecting the delivery of the medication to the disease cells by application of the magnetic field and directing the particles into or adjacent the diseased cells by magnetic navigation.

Alexiou et al. teach using magnetic nanoparticles surrounded by starch polymers bound to mitoxantrone (MTX) a chemotherapeutic agents that inhibits DNA and RNA synthesis to treat squamous cell carcinoma by magnetically targeting the MTX- magnetic nanoparticles to the tumors, see Abstract, Materials and Methods, and Figures. Alexiou et al. teach administering the nanoparticles by intravenous intra-arterial infusion, see Table 1. Alexiou et al. teach that magnetic drug targeting leads to uptake of the particles by cells, see Figure 3 and 4. Thus, the method of Alexiou et al is a method of magnetic transfection.

8. Claims 1-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Alexiou et al. (Cancer Research Dec. 2000, 60: 6641-6648) as evidenced by Alexiou et al. (J. Drug Targeting, April 2003, 11: 139-149).

The claims are drawn to a method of treating diseased cells in a human or other animal body comprising the steps of: providing particles comprising one or more nanoparticles of magnetic material, wherein the particles comprise medication introducing the particles into the

body; directing the particles into or adjacent the diseased ceils; and applying a magnetic field to the magnetic nanoparticles to treat the diseased cells by magnetically induced motion of the nanoparticles or by magnetically induced release of the medication.

It is noted that given that claims encompass effecting the delivery of the medication to the disease cells by application of the magnetic field and directing the particles into or adjacent the diseased cells by magnetic navigation, thus the treatment of the diseased cells by magnetically induced motion of the nanoparticles encompasses effecting the delivery of the medication to the disease cells by application of the magnetic field and directing the particles into or adjacent the diseased cells by magnetic navigation.

Alexiou et al. (2000) teach using magnetic nanoparticles surrounded by starch polymers bound to mitoxantrone (MTX) a chemotherapeutic agents that inhibits DNA and RNA synthesis to treat squamous cell carcinoma by magnetically targeting the MTX- magnetic nanoparticles to the tumors, see Abstract, Materials and Methods, and Figures. Alexiou et al. (2000) teach administering the nanoparticles by intravenous intra-arterial infusion, see Table 2. Alexiou et al. (2000) teach that the magnetic particles can be modified with monoclonal antibodies, lectins, peptides, hormones, or genes to make delivery of the compounds more efficient and highly specific, see p. 6648-1st col.

Alexiou et al. (2003) teach that magnetic drug targeting leads to uptake of the particles by cells, see Figure 3 and 4. Thus, the method of Alexiou et al (2000) is a method of magnetic transfection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 16, 17, 22, 24, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexiou et al. (Cancer Research Dec. 2000, 60: 6641-6648) as applied to claim 1-11 above, in view of Chung et al. (J. Controlled Release 2000 65: 93-103), in view of Jordan et al.

(J. Magnetism and Magnetic Materials, 2001 225:118-126, IDS), and in view of Shinkai et al. (Jpn. J. Cancer Res. 92:1138-1146).

9. Alexiou et al. teach as set forth above and teach localizing the magnetic particles with MRI after application of the magnetic field, see Fig. 16. Alexiou et al. do not teach particles that comprise a heat sensitive reservoir of medication, that the application of the magnetic field to the nanoparticles provides heat to effect delivery of the medication and/or to damage the disease cells by heat, or a magnetic field that is an AC magnetic field at a frequency in range of 1KHz to 5 MHz. Alexiou et al. do not teach confirming the adjacency of the particles to diseased cells or tissue prior to applying the magnetic field by MRI imaging.

Chung et al. teach thermo-sensitive polymeric micelles comprised of AB block copolymers of PIPAAm with either poly(butly methacrylate or polystyrene for the thermo-responsive drug delivery of adriamycin to cells, see Abstract, Fig. 4 and 5 and table 1. Chung et al. teach that the thermo-responsiveness of the micelles can increase the targeting efficiency via a stimuli-responsive targeting process that utilizes local heating at solid tumor sites. Chung et al. teach that the thermo-response is expected to exhibit multiple targeting functions: a passive and a stimuli-responsive targeting mechanism, plus the therapeutic effect of hyperthermia by local heating, see p. 94 1st col. Chung et al. teach that hyperthermia enhances the cytotoxicity of some anticancer drugs by synergistic effects, see p. 94- 2nd col. Chung et al. teach that thermo-sensitive lipsosomes have been used to achieve targeted drug delivery, see p. 94- 2nd col.

Jordan et al. teach that hyperthermia intensifies the efficacy of radiation and/or chemotherapy, see pp.118-119, Introduction and state of the art. Jordan et al. teach that ferromagnetic seeds can be used to induce localized hyperthermia with AC magnetic field of 25-

50 kHz, see p. 119-2nd col. Jordan et al. teach using magnetic nanoparticles to induce hyperthermia in tumors with a device using a 100 kHz AC magnetic field, see section 3, pp. 120-124 and Fig. 2-3.

Shinkai et al. teach that hyperthermia is a therapy based on the fact that tumor cells are more sensitive to temperature in the range of 42-45°C than normal tissues, see p. 1138. Shinkai et al. teach using antibody targetd magnetoliposomes to induce hyperthermia with a 118 kHz AC magnetic field to treat renal cell carcinomas in mice, see Abstract, Materials and Methods, Figs. 4-7 and Tables 1-2.

It would have been *prime facie* obvious at the time the invention was made and one of skill in the art would have be motivated to combine the teachings of Alexiou et al. and Chung et al. and substitute the starch polymers bound to medicine around the nanoparticles with the thermo-sensitive copolymers bound to medicine of Chung et al. to provide greater control of the timing of the release of the drug upon providing an appropriate increase in temperature by magnetic field induced hyperthermia. Furthermore, one would have been motivated to use a heat induced drug release because Jordan et al. and Chung et al. teach hyperthermia intensifies the efficacy of radiation and/or chemotherapy and Shinkai et al. teach that hyperthermia induced in magnetic particle is effective for cancer treatment. Additionally, it would have been *prime facie* obvious at the time the invention was made and one of skill in the art would have be motivated to use an AC magnetic field in the frequency range of 1 KHz-5MHz because Jordan et al. and Shinkai et al. teach that AC magnetic fields in this range are routinely used in the art for the induction of magnetic hyperthermia. Furthermore, it would have been *prime facie* obvious at the time the invention was made and one of skill in the art would have be motivated to confirm the

adjacency of the magnetic nano-particles loaded with medication in a thermo-sensitive reservoir to the tumors using MRI to ensure the proper localization of the magnetic particles to the disease tumor tissue before thermally inducing the release of the drug with a AC magnetic field to prevent non-specific release of the drugs in normal tissues if the nano-particles have not been properly localized. Thus, given the above, one of skill in the art would have been motivated with a reasonable expectation of success to make and used the claimed method.

10. No claims allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to PETER J. REDDIG whose telephone number is (571)272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Helms Larry can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/
Examiner, Art Unit 1642